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The history of rabies in the Western Hemisphere

Andres Velasco-Villa, Ph.D.^{a,*}, Matthew R. Mauldin^{a,b}, Mang Shi^c, Luis E. Escobar^d, Nadia F. Gallardo-Romero^a, Inger Damon^a, Victoria A. Olson^a, Daniel G. Streicker^{e,f}, and Ginny Emerson^a

^aDivision of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd, NE, Atlanta, 30329, GA, USA

^bOak Ridge Institute for Science and Education (ORISE), CDC Fellowship Program, Oak Ridge, TN, USA

^cCharles Perkins Centre, School of Life and Environmental Sciences and Sydney Medical School, The University of Sydney, Sydney, NSW, 2006, Australia

^dDepartment of Fisheries, Wildlife and Conservation Biology, University of Minnesota, Saint Paul, 55108, MN, USA

^eInstitute of Biodiversity, Animal Health and Comparative Medicine, University of Glasgow, Graham Kerr Building, Glasgow, G12 8QQ, Scotland, UK

^fMRC-University of Glasgow Centre for Virus Research, Sir Henry Wellcome Building, Glasgow, G61 1QH, Scotland, UK

Abstract

Before the introduction of control programs in the 20th century, rabies in domestic dogs occurred throughout the Western Hemisphere. However, historical records and phylogenetic analysis of multiple virus isolates indicate that, before the arrival of the first European colonizers, rabies virus was likely present only in bats and skunks. Canine rabies was either rare or absent among domestic dogs of Native Americans, and first arrived when many new dog breeds were imported during the period of European colonization. The introduction of the cosmopolitan dog rabies lyssavirus variant and the marked expansion of the dog population provided ideal conditions for the flourishing of enzootic canine rabies. The shift of dog-maintained viruses into gray foxes, coyotes, skunks and other wild mesocarnivores throughout the Americas and to mongooses in the Caribbean has augmented the risk of human rabies exposures and has complicated control efforts. At the same time, the continued presence of bat rabies poses novel challenges in the absolute elimination of canine and human rabies. This article compiles existing historical and phylogenetic evidence of the origins and subsequent dynamics of rabies in the Western Hemisphere, from the era preceding the arrival of the first European colonizers through the present day. A companion article reviews the current status of canine rabies control throughout the Western Hemisphere and

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*Corresponding author: Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases, Division of High-Consequence Pathogens and Pathology, Poxvirus and Rabies Branch, 1600 Clifton Rd, NE MailStop G06, Atlanta, GA, 30333, USA. Tel.: +1 404 639 1055., DLY3@CDC.GOV (A. Velasco-Villa).

steps that will be required to achieve and maintain its complete elimination (Velasco-Villa et al., in press).

1. Introduction

This article reviews current knowledge of the history of rabies in the Western Hemisphere (WH), based on historical records and phylogenetic analyses of the diversity of rabies lyssaviruses (RABLV) circulating in dogs, wild terrestrial mesocarnivores and bats. A companion paper (Velasco-Villa et al., in press) summarizes the status of canine rabies control in the WH, including a discussion of measures that will be required to achieve and maintain elimination throughout North, Central and South America and the Caribbean islands.

We first provide basic information on lyssaviruses and RABLV, then review what is known about rabies during the period of Native American habitation. We then examine the impact of European colonization, which resulted in the importation of many new dog breeds, an “explosion” of the dog population and the introduction of the cosmopolitan dog rabies variant. After bringing the history through the present day, we describe how dog-maintained rabies has spread to wild mesocarnivores (coyotes, skunks, gray foxes and mongooses), and how continued circulation in these species complicates control efforts. We also note that the widespread presence of rabies virus in bats poses novel challenges for the complete elimination of the disease in humans.

2. Background information and definitions

2.1. The lyssaviruses

Rabies is an acute, highly lethal encephalomyelitis caused by viruses in the genus *Lyssavirus*. Current theories agree that the lyssaviruses probably originated in Old World bats (Banyard et al., 2014; Kuzmin et al., 2011; Rupprecht et al., 2011; Hayman et al., 2016), which are confirmed reservoir hosts for 14 of the 16 known viral species. Dog-maintained rabies lyssavirus (RABLV) occurs globally, but RABLV associated with bats is only found in the New World (Kuzmin et al., 2011; Walker et al., 2015). The non-rabies lyssaviruses have been implicated in only a handful of infections of humans, domestic animals, and wildlife (Banyard et al., 2014). In contrast, RABLV lineages maintained and transmitted by domestic dogs cause more than 60,000 deaths annually across the globe, with the majority of cases occurring in Asia and Africa (Hampson et al., 2015; Shwiff et al., 2013).

In this paper, we define “dog-maintained viruses” as those which are perpetuated between ill and healthy dogs exclusively. In contrast, “dog-derived” viruses are those which were formerly dog-maintained lineages that have spilled over and become established within a specific population of wild terrestrial meso-carnivores, in which transmission cycles become independently perpetuated (Velasco-Villa et al., 2008a,b). Similarly, “bat-maintained viruses” are those that circulate endemically in different species of bats. Bat-maintained RABLV have a characteristic genetic makeup shaped by establishment in a specific species

of bat. Thus, there are multiple bat-maintained RABLV variants and lineages circulating in a variety of bat species throughout different regions of the Americas. Conversely, bat-derived viruses are those that have been shown by phylogenetic analysis to be descended from bat-maintained variants or lineages, but have become established in populations of wild mesocarnivores that now maintain independent rabies enzootics. The lower part of Fig. 1 displays some examples of the former and the latter.

2.2. Current limitations to defining an accurate evolutionary timeline for lyssaviruses

Limitations on the assessment of the actual evolutionary time-scale of lyssaviruses hamper accurate estimations of how long lyssaviruses or RABLV could have been present in the world. Time-scale calculation flaws are mainly imposed by available sequence data that only encompass the recent evolutionary history of the virus, and by a poor taxa sampling that only comprises a small portion of the extant viral diversity (Plyusnin and Sironen, 2014; Sharp and Simmonds, 2011). Thus, currently available sequence data sets only allow reconstruction of recent divergence histories that represent snapshots of the past 800–1200 years of the overall evolutionary history of these viruses (Badrane and Tordo, 2001; Bourhy et al., 2008; Holmes et al., 2002; Hughes et al., 2005; Kuzmina et al., 2013; Streicker et al., 2012a,b; Hayman et al., 2016). Because it is not possible to recover samples of viruses millions of years old, more accurate time scales for the evolutionary history of the lyssaviruses cannot be determined. Furthermore, it is pertinent to clarify that the availability of ancient historical documents on the occurrence of a specific infectious disease does not imply that the date of its origins is necessarily known. It may simply support arguments of probable older origins.

2.3. The origin of rabies lyssavirus

Phylogenetic reconstructions of extant lyssaviruses suggest that the most recent common ancestor of RABLV underwent a host change at least twice, once into New World bats and once into dogs (Badrane and Tordo, 2001). If dogs originated in the Old World, it is parsimonious to suggest that RABLV first came into contact with dogs in a domestication point in Europe or Asia (Grimm, 2015). Once RABLV had become established in dogs and the bond between dogs and humans had strengthened, favoring a massive increase in the dog population, rabies epizootics and epidemics flourished across Eurasia and Africa (Fig.1) (Bourhy et al., 2008; Leonard et al., 2002; Van Asch et al., 2013).

RABLV has the widest host range of all the lyssaviruses, with documented reservoir hosts occurring in a variety of species in multiple mammalian orders (*Chiroptera*, *Carnivora*, *Primates*). Given a clear predominance of bats as reservoir hosts of lyssaviruses, it is likely that the reservoir species of the most recent common ancestor of RABLV was an Old World bat, with the virus eventually becoming sustained in both Old World dogs and New World bats. There is uncertainty regarding when, where, and how this host shift occurred, as well as the geographic dispersal of RABLV throughout the Old World terrestrial carnivores and New World bats. However, the fact that a host shift from a bat-associated lyssavirus to a terrestrial carnivore occurred at least once sets a precedent for such an event (Badrane and Tordo, 2001). Given ideal conditions, it is therefore possible for such an event to be repeated, either by a RABLV variant/lineage or another lyssavirus species, as it has been described in the

Americas (Aréchiga Ceballos et al., 2010; Condori-Condori et al., 2013; Kuzmin et al., 2012; Velasco-Villa et al., 2008a).

Global phylogenies encompassing all extant dog-maintained and dog-derived RABLV variants and lineages divide them into two groups, the cosmopolitan group and the Old World group (Fig. 1) (Bourhy et al., 2008; Velasco-Villa et al., 2008b). The cosmopolitan group comprises a monophyletic assemblage of dog-maintained and dog-derived RABLV variants mainly enzootic across Europe, Africa, Central Asia, the Middle East and the Americas. Whereas, the Old World group encompasses a more complex assemblage of RABLV with independent endemic distribution across the Arctic Circle, Southeast and Central Asia, South Central Africa, and West Africa, which are paraphyletic with respect to the cosmopolitan group (Figs. 1 and 2). (Bourhy et al., 2008; Velasco-Villa et al., 2008b).

The disproportionate health impact of RABLV compared to other lyssavirus species is primarily due to its successful establishment in domestic dogs and multiple species of terrestrial mesocarnivores. The earliest record of a disease affecting humans with signs and symptoms consistent with rabies (including an association with dog bites) is found in the Eshnunna cuneiform law tablets from ancient Mesopotamia, Middle East, dating back to the 18th-19th centuries BC (Fales, 2010). Subsequent historic records from Greece, Rome, China and other ancient and contemporary cultures all across Eurasia have mentioned a disease transmitted to humans through contact with mad dogs.

2.4. Host switching

A RABLV variant is operationally defined as a genetically distinct virus based on nucleotide sequence data, which in a phylogenetic tree segregate in highly supported monophyletic clusters at most external nodes that in turn are often associated with a specific mammal species. Lineages are defined as discrete monophyletic clusters at more internal nodes associated with the same taxonomic group (e.g. multiple geographic variants of dog-maintained RABLV or multiple variants of bat-maintained RABLVs) that have a well-defined circumscribed geographic distribution (Velasco-Villa et al., 2008b). A single lineage may therefore contain multiple variants.

During the course of their existence, several RABLV variants and lineages of both dog and bat origin have switched hosts into a wide variety of wild mesocarnivores (Badrane and Tordo, 2001; Kuzmin et al., 2012; Mollentze et al., 2014; Smith, 2002; Smith et al., 1992). During this process, a RABLV variant establishes a species-specific relationship with its reservoir host that compartmentalizes the disease within geographically discrete enzootics, forming a new variant that in turn may affect other susceptible mammal species in its surroundings (Smith and Seidel, 1993).

3. Rabies in the Western Hemisphere

3.1. During Native American habitation, before the arrival of Europeans

According to the most recent archeological evidence, colonization of the Americas began approximately 12,500 to 15,000 years ago by south Siberian Paleo-Indians through an unglaciated corridor at the Bering Strait (Harcourt, 2016; Pedersen et al., 2016). Recent

phylogenetic studies based on extant RABLV diversity in New World bats and skunks suggest that the presence of rabies in the WH predated the dawn of European transoceanic travel in the 15th century (Badrane and Tordo, 2001; Kuzmina et al., 2013; Velasco-Villa et al., 2008b).

The earliest archeological findings, together with ancestral phylogenetic reconstructions, indicate that Asian dogs brought by humans colonized the WH from 8500–10,000 years ago (Grimm, 2015; Van Asch et al., 2013). Pre-Columbian American cultures frequently portrayed images of bats and dogs in codices and monoliths, but it is believed the meaning of these historical monuments has often been religious, rather than representing known sources of infectious diseases (Vos et al., 2011).

At the end of the 16th century a Spaniard, Francisco Hernandez, published a comprehensive compilation of the animals and plants found in most of North America (excluding Alaska, Greenland, and parts of northern Canada), Central America, the Caribbean and portions of northern Colombia and Venezuela, entitled “Historia natural de los animales de la Nueva España”, in which he did not describe or report any rabies cases. Hernandez would have been familiar with dog-maintained rabies, as it was widespread in Spain at that time, and he would therefore have reported it had he seen in the New World (Vos et al., 2011).

3.1.1. Rabies in bats—Some documents published in the early 16th century by Spanish colonizers seem to indicate the presence of vampire bat-associated rabies in the Americas. These narratives refer to people and livestock having been attacked furiously by blood-sucking bats at “twilight”, and how these encounters frequently resulted in death (Vos et al., 2011). The most prominent authors of the time, Petrus Martyr D'Agheira (1516), Francisco Montejó (1527), De Oviedo (1526), and Girolamo Benzoni (1565) referred to diseases associated with bats in their writings (Baer and Smith, 1991; Steele and Fernandez, 1991; Vos et al., 2011). These historical accounts of the putative existence of bat-associated rabies in the WH have been corroborated by phylogenetic reconstructions (Hughes et al., 2005; Kuzmina et al., 2013; Streicker et al., 2016).

Due to the furious and unprovoked nature of rabid dog attacks and traditional knowledge of the association of dog bites with rabies, it is unlikely that, had dog-associated rabies been present in the New World at the time of European colonization, it could have gone unnoticed for more than 200 years. This contrasts with the situation for bat-associated rabies, since despite all technological and diagnostic advances to date, the various, subtle routes of exposure to bat-associated rabies may cause the disease still to go unnoticed (for example, failure to report a history or recognize a bat bite has led to organ transplantations from patients who have died from atypical rabies) (Basavaraju et al., 2014; De Serres et al., 2008). From a broad epidemiologic perspective, bat-associated rabies cases are rare in the Americas (Basavaraju et al., 2014), as recent estimates of incidence range from 2.2–6.7 human cases per billion persons/year over a 57-year period in Canada and the United States (De Serres et al., 2008). Given the low incidence and nature of human-bat interactions, it is not unreasonable to think that if bat-associated human rabies cases occurred in the pre-Columbian Americas, the connection between rabies and bats could easily have gone unnoticed, leaving no historical trace.

3.1.2. Arctic fox rabies—Given the contemporary geographic ranges of viruses and reservoirs, the only currently extant dog-derived RABLV variant that could have reached the WH by natural means before European colonization is the arctic fox RABLV variant. This observation is based on the Holarctic distribution of *Vulpes lagopus*. However, the earliest reports of a rabies-like disease affecting sled dogs in northern Greenland only date back to 1859–64 (Humphrey, 1971; Johnson, 1971; Steele and Fernandez, 1991). Beginning in the early 1900s, a massive rabies epizootic killed a significant portion of the arctic fox population, but it was not until the development of molecular techniques and phylogenetic analysis that the arctic fox RABLV variant was confirmed to be enzootic throughout the entire circumpolar region (Hanke et al., 2016; Kuzmin et al., 2008; Nadin-Davis et al., 2012).

Phylogenetic reconstructions suggest that the introduction of RABLV into arctic foxes may have resulted from the northern spread of the arctic-like RABLV variant, which circulates among dogs in Central and Far East Asia (Kuzmin et al., 2008; Nadin-Davis et al., 2012). Contemporary arctic fox and the arctic-like RABLV variants can only be traced back until the 1600's, indicating the arctic fox RABLV variant likely could have not reached the WH before European colonization (Hanke et al., 2016; Kuzmin et al., 2008). Furthermore, global RABLV phylogenies demonstrate that the arctic fox RABLV is more closely related to the cosmopolitan dog lineage than to autochthonous terrestrial carnivore-maintained New World RABLV such as the bat-maintained or the skunk bat-related RABLV variants. Thus far, all evidence suggests that the arctic fox RABLV variant has not yet become established in wild mesocarnivore populations with an exclusive natural distribution in the WH (Figs. 1 and 2) (Velasco-Villa et al., 2008b).

3.1.3. Canine rabies—Although dog populations that entered the Americas with humans are thought to have overlapped geographically and temporally with RABLV variants circulating in bats and skunks, the WH was apparently free of canine rabies when the first Europeans arrived, and that situation continued for more than two centuries (Badrane and Tordo, 2001; Velasco-Villa et al., 2008b). What factors might have kept the Americas free of enzootic dog-maintained rabies for such a long period of time?

The absence of dog-maintained RABLV lineages in pre-Columbian times clearly played a critical role in maintaining a dog rabies-free status after the arrival of Europeans. However, it is interesting that the niche which was eventually occupied by the cosmopolitan dog variant might have been filled earlier by the movement of bat and skunk/raccoon associated lineages into dog populations. Phylogenetic reconstructions make it clear that such transfers did not occur: all putative autochthonous RABLV variants associated with New World bats, skunks, and raccoons are genetically distinct from all extant dog-maintained and dog-derived RABLV variants of the world (Badrane and Tordo, 2001; Smith et al., 1992; Velasco-Villa et al., 2008b). As can be seen clearly in Figs. 1 and 2, the cosmopolitan dog lineage represents introduction of dog-maintained RABLV into the WH, Africa and the Middle East around the time of the European commerce and industrial revolutions. If dog-maintained RABLV existed in the WH before the European colonization, there should be extant RABLV lineages in the WH whose sequences would fall in phylogenetic reconstructions out of the

cosmopolitan group, but somewhere along with the Old World dog-maintained RABLV group or alternatively within the bat-maintained or bat-related RABLV group.

Low dog population density is another possible reason why dog-maintained rabies was absent from the pre-Columbian Americas. Keeping free-roaming dog populations low constitutes one of the paramount strategies to sustain rabies control and long-term elimination (Lembo et al., 2012). At the time of the European conquest, native dogs were widespread, but population numbers remained low (Vos et al., 2011). This demographic hypothesis is supported by restricted haplotype diversity found in ancient New World dog breeds (Leonard et al., 2002; Van Asch et al., 2013).

Despite the increased interaction/commensalism between native dogs and pre-Columbian human societies of the Americas, abundant evidence indicates that breeds from different regions rarely interbred, either because they remained attached to their communities or they were exclusively traded as a food source (Van Asch et al., 2013). Research has found little or no evidence of genetic admixture between various New World dog breeds or other sympatric canids (Grimm, 2015; Leonard et al., 2002; Van Asch et al., 2013). These data, along with the lack of a pre-Columbian dog population explosion, contrasts with the demographic history of dogs in the Old World (Leonard et al., 2002). Distinct cultural differences in the roles of dogs (e.g., their use for religious and medicinal purposes in the New World) could have influenced the presence of dog-maintained rabies in pre-Columbian dogs, so that it never became epizootic or epidemic. Nevertheless, the existence of sporadic pockets of dog rabies due to putative autochthonous RABLV variants during this period cannot be ruled out. Rabies outbreaks have been known to “fade out” even in the absence of control measures, probably due to limited opportunities for disease transmission within potential new reservoir host populations. Conversely, low levels of “native” disease could have been out-competed by other pre-Columbian RABLVs or by the cosmopolitan RABLV lineage upon its introduction, thus explaining why many more RABLV lineages associated with terrestrial carnivores are not seen in the Americas today.

3.2. Introduction of canine rabies during European colonization and its consequences

For more than two centuries after the arrival of the Spanish “conquistadors” and their canine companions, historical records indicate that dog-maintained rabies was either unnoticed or absent. Similarly, it was not until regular importation of dogs began in the late 16th and early to mid-17th centuries that dog overpopulation became a public health problem in the New World due to an increase in transmission of zoonotic diseases and to greater numbers of people attacked by packs of stray dogs (Lucas et al., 2008; Secretaría de Salud, 2001; Smith et al., 1992). Dating analyses have estimated that dog-maintained and dog-derived RABLV variants and lineages did not enter the WH before the period 1642–1782 (95% high probability density interval) (Fig. 2) (Badrane and Tordo, 2001; Bourhy et al., 2008).

Because the incubation period of rabies in dogs typically ranges from 3-8 weeks, decreasing trans-Atlantic travel times probably played an important role in the importation of dog-maintained RABLV variants into the WH, as propelling technologies and routes improved. In the 1500s, six or more months sailing was not unusual to reach the Western Hemisphere from the Old World. In the 1600s, the average time shortened to three months, and by the

1800s 2–3 weeks. By the turn of the 20th century, 3–5 days was an average time to cross the Atlantic, increasing the likelihood of importation of rabies-infected dogs as incubation times ranges from 3 to 8 weeks. Thus, decreasing crossing times by trans-Atlantic liners also increased the importation of both healthy and infected dogs, further facilitating the introduction of dog-maintained RABLV into the WH (Hugill, 1993; Rodrigue, 2016).

The first dog-maintained rabies epizootic in the WH was recorded in Mexico City in 1709, followed by the first documented occurrence of the disease in humans in the Greater Antilles during the period 1776–78 (Lucas et al., 2008; Steele and Fernandez, 1991; Vos et al., 2011). These outbreaks in dogs and humans increased both in frequency and in geographic distribution throughout the early 1800s, occurring in Peru (1803), Argentina (1806), and Chile (1835), and eventually becoming common throughout the Americas (Steele and Fernandez, 1991; Smith et al., 1992).

The deleterious consequences of the introduction of European domestic dogs for both human and dog populations of the WH are indisputable (Van Asch et al., 2013). The quantitative impact of this invasion can be measured by the extent of allelic replacement and genetic admixture within the genomes of modern-day dogs. Gene pool comparisons between ancestral and contemporaneous aboriginal dog breeds demonstrate that the Inuit, Canadian Eskimo, Greenland dog, and Mexican Chihuahua remained pure breeds after European colonization, whereas Central and South American breeds had ~30% European female lineages, suggesting a marginal replacement due to cross-breeding with European dogs (Leonard et al., 2002; Van Asch et al., 2013). In similar studies, contemporary free-roaming and village dogs were analyzed to assess the overall intermixing that might have occurred with aboriginal breeds. Feral dogs in most large Latin American cities exhibited an almost complete replacement (~80%) of native alleles with those of European dog breeds. A similar pattern, albeit to a slightly lesser extent (70–80% replacement), was observed in more remote areas.

4. Spillovers of dog-maintained rabies viruses to other terrestrial carnivores

It was not until the advent of molecular diagnostic and virus typing techniques in the late 1970s that rabies epizootics in wildlife began to be noticed. However, it is now universally recognized that one of the most important consequences of long-term dog-maintained rabies enzootics has been the large-scale geographic establishment of rabies in wild mesocarnivores (Bourhy et al., 2008; Liu et al., 2010; Sabeta et al., 2007; Smith et al., 1992; Velasco-Villa et al., 2008b; Zulu et al., 2009).

The presence and origins of rabies in wild terrestrial mesocarnivores worldwide following the successful control and elimination of dog-maintained rabies have been examined through molecular epidemiological and phylogenetic studies, which have unveiled a consistent common ancestry between dog-maintained RABLV and the newly dog-derived RABLV variants maintained in red and gray foxes, skunks, ferret badgers and other species (Figs. 1 and 2) (Velasco-Villa et al., 2008b). Several RABLV variants that originated in this way are

most closely related to, and are most likely derived from dog-maintained variants circulating in the same region (Carnieli et al., 2013; Chiou et al., 2014).

Modern ancestral reconstruction methods have become instrumental in estimating an approximate date for the emergence of most dog-derived RABLV variants around the world (Hanke et al., 2016; Hughes et al., 2005; Lin et al., 2016). Estimated dates based on sequence data (phylogenetic methods) are often more recent than the first historical records, which may be due to assumptions built into molecular clock analyses (e.g., viral isolation dates, taxonomic sampling, sampling distributions of calibration nodes), loss of historical data (viral isolates or documentation either not kept or lost due to unusual circumstances) or cryptic circulation of RABLV in sylvatic animals.

According to rough molecular clock estimates, the RABLV cosmopolitan variant diverged and became established in multiple species of mesocarnivores across the Old World, the Americas and the Caribbean region in the 1700s, with a 95% probability density interval, indicating a most likely period of spread between 1642 and 1782 (Fig. 2) (Kobayashi et al., 2011). The following sections review recognized, well-established epizootics of dog-derived RABLV in skunks, coyotes, gray foxes and mongooses.

4.1. Skunks

The first rabies epizootic in terrestrial wild life was documented in the USA in spotted skunks (*Spilogale putorius*) in 1826 (Johnson, 1971). Its timing suggests these records could have been associated with the California skunk RABLV variant or the Baja California Sur Mexico skunk RABLV variant. The latter seems to be the earliest lineage of the cosmopolitan clade in phylogenetic reconstructions (Fig. 2). Multiple, widespread dog-derived skunk rabies epizootics have been reported since 1960 in the Baja California Peninsula of Mexico, California and the north-central region of the USA (Dyer et al., 2014; Smith et al., 1992; Velasco-Villa et al., 2008b). Nonetheless, these early rabies outbreaks in skunks could have been related to the bat-derived skunk RABLV variant, which could have become established much earlier than European colonization and is still circulating in striped skunk (*Mephitis mephitis*) populations across the south-central USA and in spotted skunk (*Spilogale putorius*) populations across north-central Mexico. Unfortunately, there are no archival samples to prove which variants actually caused these early outbreaks.

4.2. Coyotes

The first recorded epizootics of rabies in coyotes (*Canis latrans*) occurred between 1910 and 1917 in California, Oregon, Nevada, and Utah. Unfortunately, no isolates of the variant(s) circulating within the coyote populations of the region at that time were archived, making molecular characterization impossible (Humphrey, 1971). In 1994, the accidental translocation of rabid coyotes from Southern Texas into Alabama and Florida expanded an ongoing coyote rabies epizootic into the dog populations of those states (Smith et al., 1992). The coyote-dog RABLV variant appears to have the ability to be maintained and transmitted efficiently by both dog and coyote populations. Phylogenetic reconstructions revealed this coyote-dog RABLV variant to be very closely related to a dog-maintained variant that circulated in west-central Mexico until 2000, when it was eradicated (Díaz et al., 1994;

Smith, 1989; Velasco-Villa et al., 2008b). Our companion article describes the occurrence of this variant in Northern Mexico after its putative elimination from the USA and discusses its further implications.

4.3. Gray foxes

Dog-derived rabies epizootics in gray foxes (*Urocyon cinereoargenteus*) were first noticed in Burke County, Georgia, and Sabine County, Texas in 1946 and 1965, respectively, when viral typing was not yet available (Johnson, 1971). Typing techniques and molecular phylogenetics have determined that RABLV circulating in gray foxes in Arizona and central Texas were two genetically distinct RABLV variants. An archived isolate obtained from a human patient with rabies in California in 1954 suggests that the Texas gray fox variant could have been circulating in the southern USA since the 1950s or earlier (Velasco-Villa et al., 2008b). Oral rabies vaccination programs initiated in 1996 are thought to have eradicated the Texas gray fox variant, as the last reported animal with this variant occurred in 2013 (Dyer et al., 2014). However, the Arizona gray fox variant is still circulating throughout northwest-central Mexico, Arizona, and New Mexico.

Dog-maintained RABLV variants have also caused rabies epizootics in populations of gray foxes in Colombia. In the four-year period 2000–2003, 20 positive gray foxes were reported in the northern region of the country. All isolates grouped with high support to a dog-maintained RABLV variant enzootic from the same region (Paez et al., 2005). Molecular data utilized in phylogenetic reconstructions supports the hypothesis that dog-maintained rabies has been enzootic in Colombia since the early 1960s, with major epizootics occurring primarily in the 1980s, one of which caused more than two dozen human cases in 1981 (Hughes et al., 2004). The rabies situation in Colombia underlines how dramatic the urbanization of pristine wild areas and changes in land use by humans and their domestic animals, such as dogs and livestock, can directly affect sylvatic systems through the introduction of disease into native species (Paez et al., 2005).

4.4. Crab-eating foxes

Dog-maintained rabies has had similar consequences for wildlife populations in Brazil. According to recent phylogenetic reconstructions, dog-maintained rabies has been present in Brazil since European migrations took place during the late 19th and early 20th centuries. Meanwhile, major urbanization and development projects have disrupted wild ecosystems and favored the interaction of humans and their associated fauna (mainly dogs) with wildlife. Phylogenetic analyses of molecular data gathered from archived samples found that dog-maintained RABLV lineages host-shifted into crab-eating fox (*Cerdocyon thous*) populations of northeastern Brazil in the first half of the 19th century and are still circulating (Carnieli et al., 2013). Distinctive conserved mutations giving rise to fixed amino acid changes within specific regions of the nucleoprotein and glycoprotein genes of RABLV isolates from rabid crab-eating foxes, as well as their consistency over time and in the region, have also helped corroborate this host shift.

4.5. Mongooses

The problems of introduced or invasive species are not limited to the mainland of the Americas, as Caribbean islands became infested with the Indian mongoose (*Herpestes javanicus auropunctatus*) imported in 1870 to control rodents on sugar cane plantations. In the 1950s, massive rabies epizootics in these animals expanded across Puerto Rico, Cuba, Grenada, and the Dominican Republic (Johnson, 1971).

Given that rabies has been enzootic in Indian mongooses since their importation, it was once thought that epizootics in the Caribbean resulted from the introduction of infected animals from India (Smith et al., 1992). However, phylogenetic studies support the hypothesis that the mongoose RABLV variant from the Caribbean shares a most recent common ancestor with dog-maintained lineages enzootic in North America (Fig. 1) (Smith et al., 1992; Velasco-Villa et al., 2008a,b). Extensive evidence indicates that this mongoose-dog RABLV variant is maintained with equal efficiency by both dog and mongoose populations across the region, thereby complicating elimination efforts (Smith et al., 1992). Over time, the mongoose RABLV variant has evolved into a variety of distinctive lineages characteristic of the Caribbean islands where it is present, giving rise to mongoose RABLV geographic variants. In other words, the dog/mongoose RABLV variant possesses a consistent phylogeographic structure throughout countries of the Caribbean (Nadin-Davis et al., 2006; Nadin-Davis et al., 2008).

5. Spillovers of rabies viruses from bats into dogs

The role of bats as rabies reservoir hosts and their implication as an important transmission sources of this disease for terrestrial animals and humans was scientifically recognized in 1908. Carini's work published in 1911, showed for first time that vampire bats were the source of rabies virus transmission to cattle (Haup and Rehaag, 1921). The first report of a non-hematophagous bat infected with rabies virus (Brazilian fruit-eating bat, *Artibeus lituratus*) was made by Haupt and Rehaag in 1916 (Haup and Rehaag, 1921).

In the USA, rabies in bats was first discovered in Florida by Johnson in 1953. There was a subsequent boost in the number of reports in the following decade and half due to an increased interest in the problem (Johnson, 1971; Constantine, 1971). In the mid 1960's it was already suspected that rabies virus was likely maintained in several independent species-specific cycles in bats, highlighting the role of free tail bats (*Tadarida brasiliensis*), hoary bats (*Lasiurus cinereus*) and silver-haired bats (*Lasionycteris noctivagans*) (Johnson, 1971; Constantine, 1971). By 1971, 25 out of the 41 extant bat species in the U. S had been found either sporadically or enzootically affected by RABLV (Constantine, 1971).

Thus far, nearly 30 RABLV variants are associated with more than 20 species of bats across the WH. The genera *Myotis*, *Eptesicus*, and *Lasiurus* host the greatest numbers of viral variants, with 4, 5, and 6, respectively (Kobayashi et al., 2007; Kuzmina et al., 2013; Streicker et al., 2010). Several putative recurrent host shifts from bats into terrestrial mesocarnivores have been reported during the past two decades (Table 1) (Aréchiga Ceballos et al., 2010; Condori-Condori et al., 2013; Kuzmin et al., 2012; Velasco-Villa et al., 2008a).

Domestic dogs and cats have been the species most affected by bat-associated RABLV variants, particularly in countries where canine-maintained RABLV has been eliminated and mass vaccination of domestic animals has stopped (Table 1) (De Mattos et al., 2000; Dyer et al., 2014; Escobar et al., 2015; Kobayashi et al., 2007; Yung et al., 2012). However, it is worth noting that these findings are characteristic of countries with enhanced rabies laboratory-based surveillance networks, which possess the capabilities and resources to detect the circulation of bat-associated RABLV in dog and cat populations. Many countries are unable to fund such lines of investigation, especially if dog-maintained RABLV lineages have been eliminated and are no longer considered to be a major threat to human health.

Conversely, countries where only human rabies cases are typed due to local government or country-specific policies, discussed in more detail in our companion article (Velasco-Villa et al., in press). The rabies-affected human population may therefore function as sentinels, informing about RABLV variants circulating in the region.

The extent of laboratory-based rabies surveillance in wildlife varies widely from country to country. In Chile, for instance, rabies laboratories mainly test insectivorous bats, as dog-maintained rabies virus lineages have been eliminated (Escobar et al., 2015). In other countries such as Brazil and Argentina, surveillance efforts have been focused on hematophagous bats and on animals of economic importance, such as livestock (e.g., cattle and horses), reflecting a shift of priorities towards the identification of wild rabies reservoir hosts (Fig. 3).

An increased number of rabies cases, mainly associated with bat-related RABLV variants, has occurred in wild primates and mesocarnivores over the past 15 years (Table 1) (Condori-Condori et al., 2013; Favoretto et al., 2001). In Latin America and the Caribbean, a total of 218 human infections following exposure to animals other than dogs was reported in the period between 2005 and 2015 (Table 2). When broken down by country, Peru led with the largest number (99 cases). Vampire bats were responsible for or associated with the largest number (173 human infections), followed by monkeys and cats (Table 2).

Although these figures pale in comparison to the number of human infections by dog-maintained RABLV lineages, it is clear that bat-associated rabies is also affecting vulnerable human populations and their domestic animals. Furthermore, these data reflect the increasing frequency of interaction between domestic animals (especially dogs), bats and terrestrial wildlife under the current and evolving status of human demographics and culture (Escobar et al., 2015; Harcourt, 2016; Lin et al., 2016; Liu et al., 2010; Yung et al., 2012). At the same time, several Latin American countries (Argentina, Brazil, Chile, Colombia, Ecuador, Paraguay, Peru, Uruguay) with highly successful programs for the control and elimination of dog-maintained rabies have weakened or suspended canine vaccination programs, resulting in increasing numbers of rabies-susceptible dogs and cats (Escobar et al., 2015; Velasco-Villa et al., 2017 in press). This trend may allow endemic sylvatic or newly imported dog-maintained RABLV lineages to gain a foothold in dog and cat populations with waning herd immunity. Such reintroduced epizootics open additional possibilities for new outbreaks in wild carnivore species, particularly as mesocarnivores such

as urban raccoons, skunks, coyotes and foxes become more abundant in urban areas by adapting to feed on human-provided resources (Becker et al., 2015).

6. Summary and implications for the future of rabies control

Rabies lyssaviruses present in bats and skunks of the Western Hemisphere likely co-existed with domestic dogs of Native Americans for centuries, but these wildlife-associated viruses did not become established in pre-Columbian dog populations. However, the documentation of dog-maintained rabies began 200 years after the beginning of the transoceanic colonization in the late 15th century and the first importation of dogs by Europeans. This historical sequence may reflect the small size of the Native American dog population, which did not support easy transmission of the virus, detectable viral establishment or sustained circulation. Alternatively, it may have resulted from the absence of infected dogs among those imported by colonists, either through random selection or biased sampling based on the affluence of settlers, or because infected dogs died on the long journey from Europe until travel times improved. Whatever the reason, it was not until the dawn of the 18th century that massive dog-maintained rabies epizootics began to occur.

Since that time, dog-maintained rabies epizootics have had direct and indirect consequences for human populations. Domestic dogs infected both humans and terrestrial mesocarnivores such as skunks and foxes, which in turn increased the number of potential sources of human exposure. To reach its multiple current ecological niches in wildlife of the WH, the ancestor of RABLV of bats and skunks of the New World and the cosmopolitan RABLV must have undergone independent host-shift events at two clearly different time points (Badrane and Tordo, 2001; Mollentze et al., 2014), one before or during the colonization of the New World by Native Americans and the other after European colonization.

The proven ability of RABLV to become established in mammals of the orders *Chiroptera*, *Carnivora* and *Primates* suggests that it would be possible for New World bat-associated RABLV to become re-established in the increasingly unvaccinated dog populations of the modern American mainland and the islands of the Caribbean. Re-introductions of RABLV from wildlife to dogs or from remaining pockets of dog-maintained rabies into wildlife may cascade to form new wildlife rabies reservoirs, in an endless cycle. The implications of these scenarios for current and future control measures are discussed in our companion article.

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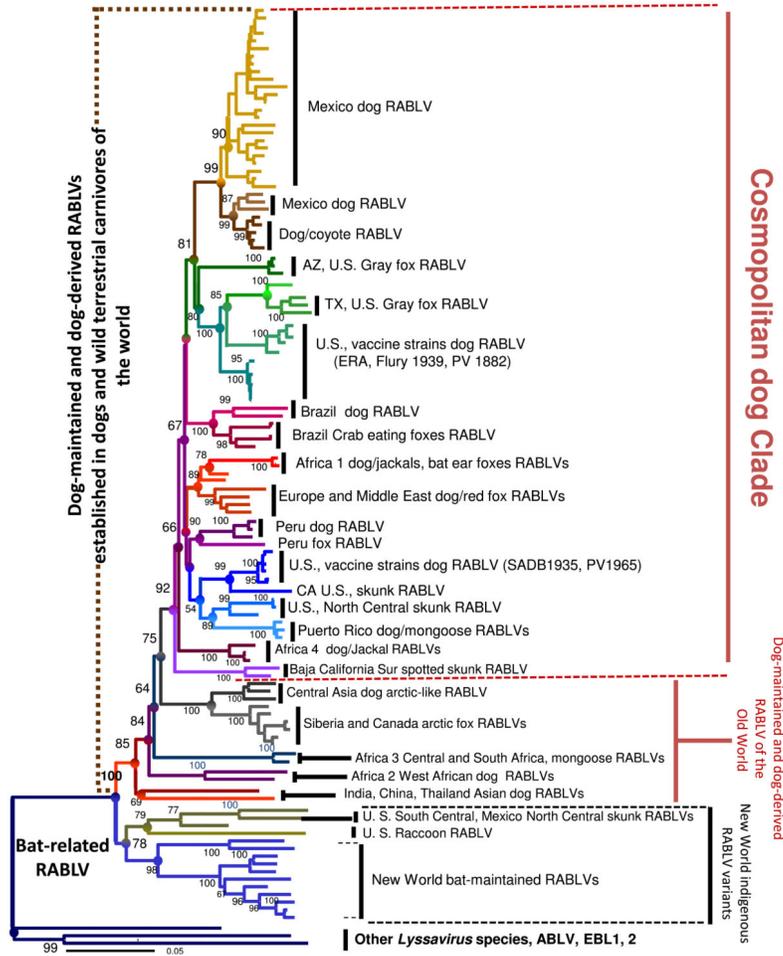


Fig. 1. Maximum likelihood phylogenetic tree of RABLV adapted from (Velasco-Villa et al., 2008b), in which relationships among major dog-maintained and dog-related variants of the world with indigenous bat-maintained and bat-related RABLV variants of the Western Hemisphere are depicted. The cosmopolitan dog group represents multiple introductions of dog-maintained RABLV from Europe into the Western Hemisphere, Africa and the Middle East and how they potentially gave rise to the establishment of epizootics in terrestrial mesocarnivores in those continents. Conversely, the Old World group demonstrates other dog-maintained RABLV introductions into Africa, Central Asia and the circumpolar region, likely coming from the Far East.

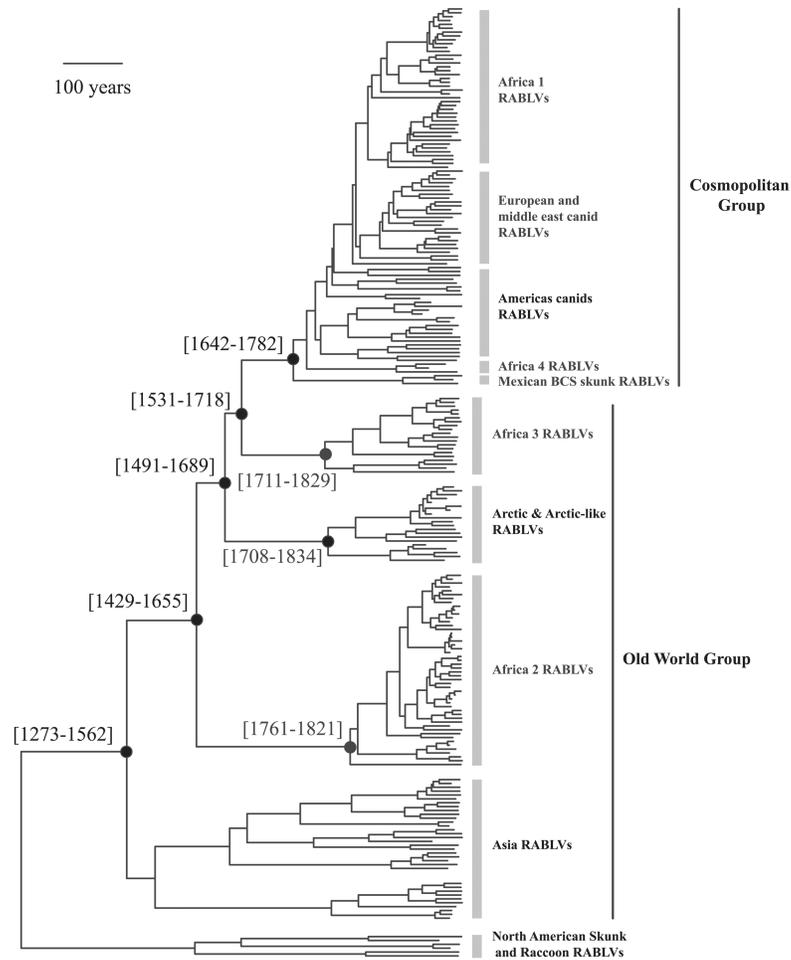


Fig. 2. Timeline of introduction of the cosmopolitan RABLV group into the Americas, Africa and the Middle East as well as introductions of more ancient Asian RABLV lineages into Africa, Central Asia and the circumpolar region. Dates in the nodes denote an estimated time period in which a common ancestor giving rise to the extant viral diversity existed. The evolutionary history of terrestrial-mammal-associated RABLVs may also be appreciated. The time-scaled phylogeny is reconstructed based on the complete nucleoprotein gene alignment, using the BEAST software package with a codon-partitioned (GTR112 + CP112 + Gamma112) substitution model and an uncorrelated log-normal relaxed molecular clock model. Estimated dates to the most recent common ancestor (MRCA), for important clades, are depicted as 95% highest posterior density intervals. For clarity, the label of each major clade is shown to the right of the phylogeny.

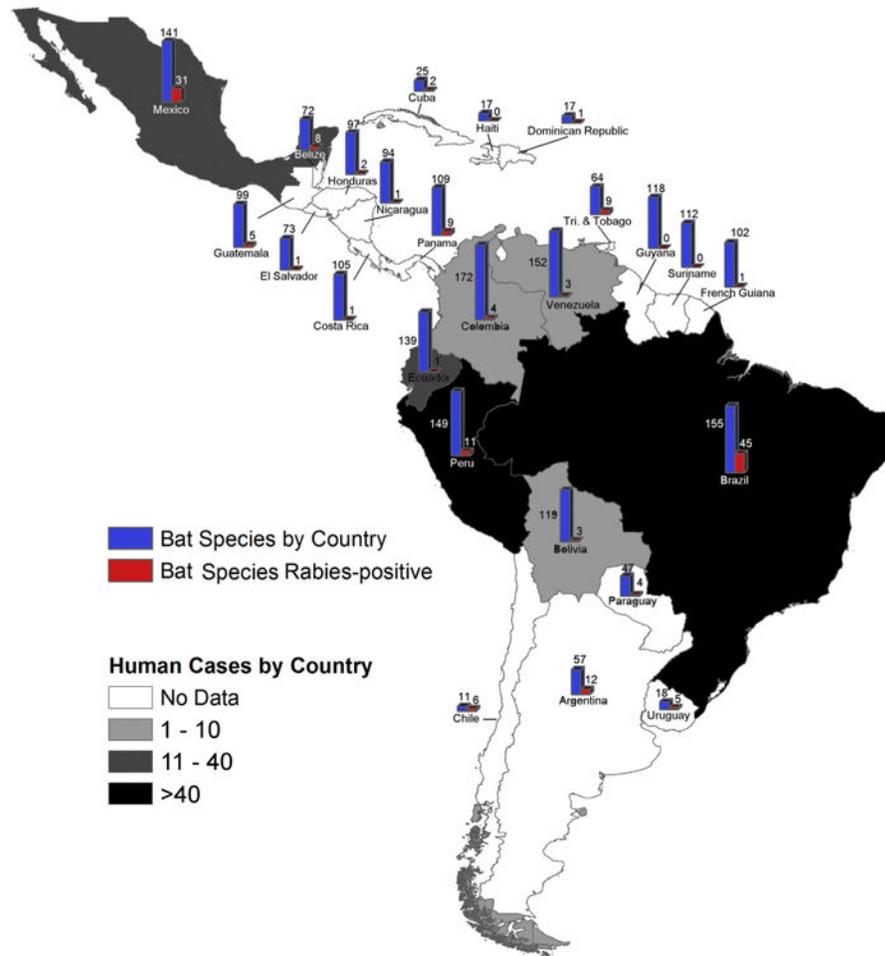


Fig. 3. Distribution of accumulated human rabies cases transmitted by bats in countries of Latin America and the Caribbean from 2005-2015. Grayscale reflects the number of laboratory-confirmed cases in which RABLV variants associated with different species of bats were identified (mainly RABLV lineages associated with vampire bats). Source: SIEPI “Especie”, <http://siepi.panaftosa.org.br/Export.aspx>. Inset blue bars represent the total number of bat species per country (or their respective bat bio-diversity), and red bars represent the actual number of species most frequently found to be rabies-positive in each country (Escobar et al., 2015).

Table 1

Accrued rabies cases caused by bat-maintained RABLV variants in Latin America and the Caribbean, grouped by host species within the period 2005–2016. The average number of annual cases are listed outside parentheses and the total samples confirmed by country within parentheses and reported to PAHO within period 2005–2016. Bats: hematophagous, insectivorous, and species not identified. Domestic animals: cattle, bison, goats, equines, llamas, sheep, swine. Wild animals: mongoose, badger, marten, otter, weasel, kinkajou, coati, raccoon, opossum, skunk, fox, lynx, coyote, wolf, bear, deer, buffalo, rabbits, beaver, squirrels. Samples for which the species was not identified were removed. Source: SIRVERA <http://siepi.panaftosa.org.br/>, accessed 2/15/17.

Country	Human	Dog	Bat	Cat	Other domestic animals	Other wildlife animals
Argentina	0 (1)	4 (4)	16 (193)	1 (6)	15 (152)	1 (11)
Belize	0 (0)	0 (0)	0 (0)	0 (0)	1 (6)	0 (2)
Bolivia	3 (31)	83 (990)	1 (6)	9 (106)	26 (256)	1 (9)
Brazil	7 (77)	25 (305)	49 (582)	5 (56)	157 (1567)	20 (239)
Canada	0 (0)	3 (37)	5 (63)	2 (25)	4 (37)	8 (92)
Chile	0 (0)	0 (2)	81 (975)	0 (1)	0 (0)	0 (1)
Colombia	2 (20)	2 (24)	0 (0)	1 (6)	82 (822)	1 (7)
Costa Rica	0 (0)	0 (0)	0 (0)	0 (0)	1 (9)	0 (0)
Cuba	0 (3)	32 (386)	2 (24)	11 (133)	8 (84)	32 (387)
Dominican Republic	1 (15)	54 (653)	0 (4)	10 (123)	5 (53)	8 (99)
Ecuador	1 (15)	0 (3)	0 (0)	0 (0)	24 (235)	0 (0)
El Salvador	1 (6)	37 (404)	1 (7)	6 (73)	14 (136)	1 (6)
Guatemala	1 (12)	37 (446)	0 (0)	2 (19)	12 (220)	0 (4)
Haiti	3 (38)	1 (6)	0 (0)	0 (0)	0 (2)	0 (0)
Honduras	0 (1)	8 (99)	0 (1)	0 (0)	1 (10)	0 (1)
Mexico	2 (28)	26 (308)	1 (16)	1 (13)	165 (1653)	7 (88)
Nicaragua	0 (0)	0 (4)	0 (3)	0 (1)	2 (17)	0 (1)
Panama	0 (0)	0 (0)	0 (0)	0 (0)	5 (46)	0 (0)
Paraguay	0 (0)	1 (10)	0 (4)	0 (2)	31 (309)	0 (5)
Peru	10 (121)	9 (107)	3 (38)	1 (8)	137 (1372)	1 (14)
Puerto Rico	0 (0)	1 (6)	0 (0)	1 (6)	1 (8)	1 (6)
Trinidad & Tobago	0 (0)	0 (0)	0 (0)	0 (0)	0 (3)	0 (0)
United States	1 (13)	2 (27)	4 (51)	3 (36)	5 (54)	

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Country	Human	Dog	Bat	Cat	Other domestic animals	Other wildlife animals
Uruguay	0 (0)	0 (0)	0 (5)	0 (0)	5 (49)	0 (0)
Venezuela	0 (4)	17 (201)	0 (0)	1 (7)	13 (128)	0 (0)

Countries of the Americas that reported cases of human rabies caused by exposure to animals other than dogs (2005-2016).

Table 2

Country	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Bolivia	1 [*]												1
Brazil	42 [*] , 1 ⁺	2 [*] , 1 [@]		1 [*] , 1 [¢] , 1 ⁺		1 ⁺ , 1 ^{**}		1 [*] , 1 ⁺ , 1 [#]	2 ⁺		1 ^{\$}	1 ^{\$}	58
Canada			1										1
Colombia	3 [*]		1 [¢]	2 ^{\$} , 1 [¢]	2 ^{\$} , 1 [*] , 1 [¢]	3 ^{\$} , 1 [¢]				1 ^{\$}			16
Dominican Republic		1 ^{\$}			1 [!]								2
Ecuador	2 [*]			1 ^{\$}			12 [*]						15
Mexico	5 ^{**} , 1 [¢]	1 ^{**}	2 [¢] , 2 [¢]	3 [*]	3 [@] , 1 [¢]	4 [*]	2 [*] , 1 [%]			1 [¢]			26
Peru	7 [*]	2 [*]	23 [*] , 1 [^]		19 [*]	13 [*]	19 [*]	10 [*]	5 [*]		3 [*]	9 [*]	111
United States	1	2 ^{**}	1 ^{**}	1 ^{**} , 1 [¢]	3	1 [*] , 1 ^{**}	4	1	1	1	1		19
Venezuela			1 [*]										1

* Hematophagous bat;

** Non-hematophagous bat;

! Bats species not reported;

⁺ Monkey;

@ Bovine;

Deer;

\$ Cat;

¢ Fox;

% Skunk;

^ Equine;

! Mongoose;

> Raccoon.

Samples for which species was not reported were removed. There were no data available for 2014. Sources: SIRVERA <http://siepi.panaftosa.org.br/>, accessed 2/15/17. Cases for the United States were complemented with data from (Dyer et al., 2014) and (Monroe et al., 2016.) Human case from Canada were collected from: <http://epe.lac-bac.gc.ca/100/206/301/cfia-acia/2011-09-21/www.inspection.gc.ca/english/anima/disejala/rabrag/statse.shtml>.

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